(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 656 206 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **95102113.8**

(51) Int. Cl.[6] **A61K 9/72**

(22) Date of filing: **08.06.92**

This application was filed on 16 - 02 - 1995 as a divisional application to the application mentioned under INID code 60.

(30) Priority: **10.06.91 US 712791**

(43) Date of publication of application:
07.06.95 Bulletin 95/23

(60) Publication number of the earlier application in accordance with Art.76 EPC: **0 588 897**

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE

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(54) Non-chlorofluorocarbon aerosol formulations.

(57) An aerosol formulation for oral and/or nasal administration is described. The formulation comprises 1,1,1,2,3,3,3 heptafluoropropane, a medicament, an excipient which is a propylene diester of a C_6-C_{12} fatty acid or a triglyceride ester of a C_6-C_{12} fatty acid and optionally a surfactant.

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INTRODUCTION TO THE INVENTION

The present invention is directed at aerosol formulations which are substantially free of chlorofluorocarbons (CFC's). More specifically, the present invention is directed at formulations substantially free of CFC's and having particular utility in medicinal applications, especially in metered dose pressurized inhalators (MDI's).

Metered dose inhalators have proven to be an effective method for delivering medicaments orally and nasally. They have been used extensively for delivering bronchodilating and steroidal compounds to asthmatics and may also be useful for delivering other compounds such as pentamidine and non-bronchodilator anti-inflammatory drugs. The rapid onset of activity of compounds administered in this manner and the absence of any significant side effects have resulted in a large number of compounds being formulated for administration via this route. Typically, the drug is delivered to the patient by a propellant system generally comprising one or more propellants which have the appropriate vapor pressure and which are suitable for oral or nasal administration. The more preferred propellant systems typically comprise propellant 11, propellant 12, propellant 114 or mixtures thereof. Often the vapor pressure of the propellant systems is adjusted by admixing a liquid excipient with the propellant.

However, propellants 11, 12 and 114 belong to a class of compounds known as chlorofluorocarbons, which have been linked to the depletion of ozone in the atmosphere. It has been postulated that ozone blocks certain harmful UV rays and that a decrease in the atmospheric ozone content will result in an increase in the incidence of skin cancer. In the 1970's certain steps were taken to reduce the CFC emissions from aerosols. Other propellants, such as hydrocarbons, were used, or the product was delivered in a different manner. Because CFC usage in medicinal applications is relatively low i.e. less than 1% of total CFC emissions, and because of the health benefits associated with metered dose inhalators, steps were not taken at that time to restrict the use of CFC propellants in metered dose inhalators.

However, continuing and more sophisticated ozone measurements have indicated that the earlier restrictions in CFC usage were insufficient and that additional, significant steps should be taken to drastically reduce CFC emissions. Recently, recommendations have been made that CFC production be virtually discontinued by the end of this century. As a result, it may not be possible to continue to use CFC propellants in the intermediate and long term. While some efforts have been made to use non-pressurized metered dose inhalators, many of these devices have not been completely successful. Many do not deliver uniform doses, are mechanically complex, do not provide the 100-200 doses per unit of current aerosol containers, are difficult for individuals to utilize, and are bulky and/or cumbersome for the patients to use, particularly when they have an acute need for the medication.

As a result, there is a need for aerosol formulations which are substantially free of CFC's. Non-CFC propellants systems must meet several criteria for pressurized metered dose inhalators. They must be non-toxic, stable and non-reactive with the medicament and the other major components in the valve actuator. One propellant which has been found to be suitable is CF_3-CH_2F-CF_3, also known as Freon 227, HFA 227, HFC 227 or 1,1,1,2,3,3,3 heptafluoropropane. However, certain physical properties, i.e., polarity and solubility, of HFC 227 differ from those of commonly used CFC propellants. Commonly used surfactants may be insoluble in HFA 227. Moreover, where the medicament is to be delivered as a solution, the medicament may not be readily soluble in this propellant. The polarity difference between HFC 227 and the previously used CFC propellants may result in a different delivery of the medicament when HFC 227 replaces a CFC propellant. The medicament may cream, settle or agglomerate in the non-CFC propellant even though this did not occur in the CFC propellant.

The use of HFA 227 previously has been disclosed for use in medicinal inhalators. European Patent Publication No. 0 384 371 is directed at the combination of propellant 227 and propane, butane, isobutane, Me_2O and/or F_2CHMe.

Research Disclosure No. 30161, May, 1989 discloses that non-CFC propellants, such as fluorohydrocarbons may be used in pressurized medicaments delivered directly to the lungs, e.g. bronchodilators.

Other publications have been directed at the use of other fluorohydrocarbons, such as HFC 134a, for aerosol propellants. European Patent Publication No. 0 372 777 is directed at medicinal aerosol formulations incorporating HFC 134a and an adjuvant having a higher polarity than the propellant. This publication lists several possible adjuvants and surfactants for use in combination with the propellant and the medicament.

International patent application No. WO 91 04011 discloses the combination of HFC 134a and a powdered medicament pre-coated with a non-perfluorinated surfactant prior to dispersing the powdered medicament in the propellant. Pages 6-7 of the publication list suitable surfactants for use with the propellant. A perfluorinated adjuvant optionally could be added. However, the pre-coating of the medicament may not be advantageous, since it adds an additional, complex step to the manufacturing process.

U.S. Patent No. 4,174,295 discloses the combination of HFC 134a with various chlorofluorocarbons and optionally a saturated hydrocarbon. U.S. Patent No. 2,885,427 discloses the use of HFC-134a as an aerosol propellant. U.S. Patent No. 3,261,748 discloses the use of HFC-134a for anesthesia. U.S. Patent Nos 4,129,603, 4,311,863, 4,851,595 and European Publication No. 379,793 also disclose the use of HFC-134a as an aerosol propellant.

However, the specific combinations noted above may not provide the desired solubility, stability, low toxicity, exact dosage, correct particle size (if suspension) and or compatibility with commonly used valves assemblies of metered dose inhalers.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed at a non-toxic formulation substantially free of CFC's having improved stability and compatibility with the medicament and which is relatively easily manufactured.

The present invention also is directed at formulations which may be utilized in present aerosol filling equipment with only relatively minor modifications and without pre-coating the medicament.

One embodiment of the present invention is directed at a formulation comprising:

A. Propellant 1,1,1,2,3,3,3 heptafluoropropane;

B. optionally an excipient selected from the group consisting of alcohols, Miglyol 812, Miglyol 840, PEG-400, menthol, lauroglycol, Vertrel 245, Transcutol, Labrafac Hydro WL 1219, perfluorocyclobutane, eucalyptus oil, short chain fatty acids, and combinations thereof;

C. a medicament; and

D. optionally a surfactant selected from the group consisting of oleic acid, sorbitan trioleate, cetyl pyridinium chloride, soya lecithin, Tween 20, Tween 60, Tween 80, Pluronic L-121 and Pluronic L-92, castor oil ethoxylate, pluronic F 68, Tetronic 150 R1 and combinations thereof.

Also included within the invention is an aerosol formulation comprising:

A. an effective amount of medicament;

B. 1,1,1,2,3,3,3 heptafluoropropane; and

C. an excipient selected from the group consisting of: propylene glycol diesters of medium chain fatty acids;
triglyceride esters of medium chain fatty acids;
perfluorodimethylcyclobutane;
perfluorocyclobutane;
polyethylene glycol;
menthol;
lauroglycol;
diethylene glycol monoethylether;
polyglycolized glycerides of medium chain
fatty acids;
alcohols;
eucalyptus oil;
short chain fatty acids;
and combinations thereof.

The formulation optionally may further comprise a surfactant. The surfactant preferably is selected from the group consisting of:
oleic acid;
sorbitan trioleate;
cetyl pyridinium chloride;
soya lecithin;
polyoxyethylene(20) sorbitan monolaurate;
polyoxyethylene (10) stearyl ether;
polyoxyethylene (2) oleyl ether;
polyoxypropylene-polyoxyethylene-ethylene diamine block copolymers;
polyoxyethylene(20) sorbitan monostearate;
polyoxyethylene(20) sorbitan monooleate;
polyoxypropylene-polyoxyethylene block copolymers;
castor oil ethoxylate; and combinations thereof.

The preferred liquid excipients are diethylene glycol monethyether, propyleneglycol diesters of medium chain fatty acids, perfluorodimethylcyclobutane and polyethylene glycol.

The preferred surfactants are oleic acid; sorbitan trioleate, cetylpyridinium chloride; polyoxyethylene (20) sorbitan monolaurate; polyoxypropylene-polyoxyethylene block copolymers; soya lecithin; and polyoxypropylene-polyoxyethylene-ethylenediamine block copolymers; with oleic acid being particularly preferred.

The invention is of particular utility where the medicament is albuterol, mometasone furoate or beclomethasone dipropionate, and salts and clathrates thereof.

A useful formulation range comprises:

A. 1,1,1,2,3,3,3 heptafluoropropane	25 - 99.99 wt %
B. medicament	0.01 - 1 wt %
C. excipient	0 - 75 wt %
D. surfactant	0 - 3 wt %

The present invention also is directed at a method of treating asthma in mammals comprising administering to a mammal in need of such treatment an effective amount of aerosol formulation comprising:

A. a medicament selected from the group comprising albuterol, mometasone furoate, beclomethasone dipropionate, and salts and clathrates thereof;

B. 1,1,1,2,3,3,3 heptafluoropropane; and

C. optionally an excipient selected from the group consisting of:
propylene glycol diesters of medium chain fatty acids;
triglyceride esters of medium chain fatty acids;
perfluorodimethylcyclobutane;
perfluorocyclobutane;
polyethylene glycol;
menthol;
lauroglycol;
diethyleneglycol monoethylether;
polyglycolized glycerides of medium chain fatty acids;
alcohols;
short chain fatty acids;
eucalyptus oil; and combinations thereof.

A surfactant optionally is present. The surfactant preferably is selected from the group consisting of:
oleic acid;
sorbitan trioleate;
cetyl pyridinium chloride;
soya lecithin;
polyoxyethylene (20) sorbitan monolaurate;
polyoxyethylene (10) stearyl ether;
polyoxyethylene (2) oleyl ether;
polyoxyethylene-polyoxypropylene-ethylene diamine block copolymers;
polyoxyethylene (20) sorbitan monostearate;
polyoxypropylene-polyoxyethylene block copolymers;
castor oil ethoxylate; and combinations thereof.

DETAILED DESCRIPTION OF THE INVENTION

The formulations of the present invention all utilize propellant 227 in combination with the medicament, optionally a liquid excipient and optionally a surfactant.

The excipient facilitates the compatibility of the medicament with the propellant and also lowers the discharge pressure to an acceptable range i.e. about 2.76 - 5.52 x 10^5 newton/meter^2 absolute (40 to 80 psia), preferably 3.45 - 4.83 x 10^5 newton/meter^2 absolute (50 to 70 psia). The excipient chosen must be non-reactive with the medicament, relatively non-toxic, and should have a vapor pressure below about 3.45 x 10^5 newton meter^2 absolute (50 psia). As used hereinafter the term "medium chain fatty acids" refers to chains of alkyl groups terminating in a -COOH group and having 6-12 carbon atoms, preferably 8-10 carbon atoms. The term "short chain fatty acids" refers to chains of alkyl groups terminating in a -COOH group and

having 4-8 carbon atoms. The term "alcohol" includes C_1-C_3 alcohols, such as methanol, ethanol and isopropanol. Among the preferred excipients are:

propylene glycol diesters of medium chain fatty acids available under the tradename Miglyol 840 (from Hüls America, Inc. Piscataway, N.J.);

triglyceride esters of medium chain fatty acids available under the tradename Miglyol 812 (from Hüls);

perfluorodimethylcyclobutane available under the tradename Vertrel 245 (from E.I DuPont de Nemours and Co. Inc. Wilmington, Delaware);

perfluorocyclobutane available under the tradename octafluorocyclobutane (from PCR Gainsville, Florida);

polyethylene glycol available under the tradename PEG 400 (from BASF Parsippany, N.J.);

menthol (from Pluess-Stauffer International Stanford, Connecticut);

propylene glycol monolaurate available under the tradename lauroglycol (from Gattefossé Elmsford, N.Y.);

diethylene glycol monoethylether available under the tradename Transcutol (from Gattefossé);

polyglycolized glyceride of medium chain fatty acids available under the tradename Labrafac Hydro WL 1219 (from Gattefossé);

alcohols, such as ethanol, methanol and isopropanol;

eucalyptus oil available (from Pluess-Stauffer International); and mixtures thereof.

A surfactant optionally may be added to lower the surface and interfacial tension between the medicament and the propellant. Where the medicament, propellant and excipient are to form a suspension, a surfactant may or may not be required. Where the medicament, propellant and excipient are to form a solution, a surfactant may or may not be necessary, depending in part, on the solubility of the particular medicament and excipient. The surfactant may be any suitable, non-toxic compound which is non-reactive with the medicament and which substantially reduces the surface tension between the medicament, the excipient and the propellant and/or acts as a valve lubricant. Among the preferred surfactants are:

oleic acid available under the tradename oleic acid NF6321 (from Henkel Corp. Emery Group. Cincinnati, Ohio);

cetylpyridinium chloride (from Arrow Chemical, Inc. Westwood, N.J.);

soya lecithin available under the tradename Epikuron 200 (from Lucas Meyer Decatur, Illinois);

polyoxyethylene(20) sorbitan monolaurate available under the tradename Tween 20 (from ICI Specialty Chemicals, Wilmington, Delaware);

polyoxyethylene(20) sorbitan monostearate available under the tradename Tween 60 (from ICI);

polyoxyethylene(20) sorbitan monooleate available under the tradename Tween 80 (from ICI);

polyoxyethylene (10) stearyl ether available under the tradename Brij 76 (from ICI);

polyoxyethylene (2) oleyl ether available under the tradename Brij 92 (from ICI);

polyoxyethylene-polyoxypropylene-ethylenediamine block copolymer available under the tradename Tetronic 150 R1 (from BASF);

polyoxypropylene-polyoxyethylene block copolymers available under the tradenames Pluronic L-92, Pluronic L-121 and Pluronic F 68 (from BASF);

castor oil ethoxylate available under the tradename Alkasurf CO-40 (from Rhone-Poulenc Mississauga Ontario,Canada); and mixtures thereof.

The medicaments of the present invention may include any pharmaceutically active compounds which are to be delivered by oral inhalation or nasally. Typical classes of compounds include bronchodilators, anti-inflammatory compounds, antihistamines, antiallergics, analgesics, antitussives, anti-anginal medications, steroids, corticosteroids, vasoconstrictors and antibiotics. Specific compounds within these classes of compounds are albuterol, mometasone furoate, beclomethasone dipropionate, isoproterenol, heparin, terbutaline, rimiterol, perbuterol, disodium cromoglycate, isoprenaline, adrenaline, pentamidine and ipratropium bromide. These compounds may be utilized either as the free base, as a salt, or as a clathrate, depending upon the stability and solubility of the active compound in the specific formulation. When clathrates are utilized, P-11 and hexane clathrates are particularly preferred.

Where the active compound forms a suspension, the particle size should be relatively uniform, with substantially all the particles preferably ranging between about 0.1-25 microns, preferably 0.5-10 microns, more preferably 1-5 microns. Particles larger than 25 microns may be held up in the oropharyngeal cavity, while particles smaller than about 0.5 micron preferably are not utilized, since they would be more likely to be exhaled and, therefore, not reach the lungs of the patient.

The formulations of the present invention may be filled into the aerosol containers using conventional filling equipment. Since propellant 227 may not be compatible with all elastomeric compounds currently utilized in present aerosol valve assemblies, it may be necessary to substitute other materials, such as

white buna rubber, or to utilize excipients and optionally surfactants which mitigate the adverse effects of propellant 227 on the valve components.

To assure uniform dispersion of the active ingredient, the formulations typically will include the following components:

	Range (wt %)	Preferred Range (wt%)	Most Preferred Range (wt%)
Medicament	0.01 - 1	0.03 - 0.7	0.05 - 0.5
Propellant	25 - 99.99	50 - 99.97	50 - 99.95
Excipient(s)	0 - 75	0 - 50	0 - 50
Surfactant(s)	0 - 3	0 - 2	0 - 1

Depending on the particular application, the container may be charged with a predetermined quantity of formulation for single or multiple dosing. Typically, the container is sized for multiple-dosing, and, therefore, it is very important that the formulation delivered is substantially uniform for each dosing. For example, where the formulation is for bronchodilation, the container typically is charged with a sufficient quantity of the formulation for 200 charges.

Suitable suspensions may be screened in part by observing several physical properties of the formulation, i.e. the rate of particle agglomeration, the size of the agglomerates and the rate of particulate creaming.settling and comparing these to an acceptable standard. Suitable solutions may be screened by observing the solubility of the medicament over the entire recommended storage temperature range.

Suspensions of the present invention preferably may be prepared by either the pressure filling or cold filling procedures well-known in the art.

For metered dose inhalators, suspensions may be particularly preferred for efficacy and stability considerations.

Those skilled in the art may choose to add one or more preservative, buffer, antioxidant, sweetener and.or flavors or other taste masking agents depending upon the characteristics of the formulation.

Examples I - XXXIII below further describe the present invention. For several of the examples, alternative formulations denoted as A and B are provided.

Component	Wt%	
	EXAMPLE I	
	A	B
Albuterol	0.5	0.1
Miglyol 812	10.0	1.0
HFC-227	89.5	98.9
	EXAMPLE II	
Albuterol	0.1	
Transcutol	25.0	
HFC-227	74.9	

EXAMPLE III

	A	B
Albuterol	0.5	0.1
Miglyol 840	10.0	1.0
HFC-227	89.5	98.9

EXAMPLE IV

Albuterol	0.1
PEG 400	1.0
HFC-227	98.9

EXAMPLE V

Albuterol	0.1
Menthol	0.5
HFC 227	98.9

EXAMPLE VI

	A	B
Albuterol	0.1	0.1
Lauroglycol	0.1	0.5
HFC 227	99.8	99.4

EXAMPLE VII

	A	B
Albuterol	0.1	0.5
Ventrel 245	10.0	49.6
HFC 227	89.9	49.9

EXAMPLE VIII

Albuterol	0.1
Labrafac Hydro WL 1219	0.5
HFC 227	99.4

EXAMPLE IX

	A	B
Albuterol	0.1	0.5
Perfluorocyclobutane	10.0	49.6
HFC 227	89.9	49.9

EXAMPLE X

	A	B
Oleic Acid	0.01	0.1
Albuterol	0.10	0.1
Ethanol	1.00	30.0
HFC 227	98.89	69.8

EXAMPLE XI

	A	B
Oleic Acid	0.01	0.1
Albuterol sulfate	0.10	0.1
Ethanol	1.00	30.0
HFC 227	98.89	69.8

EXAMPLE XII

	A	B
Oleic Acid	0.01	0.1
Albuterol	0.10	0.1
Ethanol	1.00	25.0
HFC 227	98.89	74.8

EXAMPLE XIII

	A	B
Oleic Acid	0.001	0.01
Albuterol	0.1	0.1
Miglyol 812	1.0	10.0
HFC 227	98.8	89.8

EXAMPLE XIV

Tetronic 150 R1	0.1
Albuterol	0.1
Miglyol 812	9.8
HFC-227	90

EXAMPLE XV

	A	B
Pluronic L121	0.1	0.1
Albuterol	0.1	0.1
Miglyol 812	1.0	10.0
HFC 227	98.8	89.8

EXAMPLE XVI

Tween 20	0.1
Albuterol	0.1
Miglyol 812	10.0
Vertrel 245	10.0
HFC-227	79.8

EXAMPLE XVII

	A	B
Oleic Acid	0.01	0.1
Albuterol Sulfate	0.10	0.1
Ethanol	1.00	25.0
HFC 227	98.89	74.8

EXAMPLE XVIII

	A	B
Oleic Acid	0.01	0.1
Albuterol Sulfate	0.10	0.1
Transcutol	1.00	25.0
HFC 227	98.89	74.8

EXAMPLE XIX

	A	B
Pluronic L 121	0.1	0.1
Mometasone Furoate	0.1	0.1
Miglyol 812	1.0	10.0
HFC 227	98.8	89.8

EXAMPLE XX

Tetronic 150 R1	0.1
Mometasone Furoate	0.1
Miglyol 812	9.8
HFC-227	90

EXAMPLE XXI

Mometasone Furoate	0.1
HFC-227	99.9

EXAMPLE XXII

Beclomethasone Dipropionate	0.1
HFC-227	99.9

EXAMPLE XXIII

Mometasone Furoate	0.1
Tween 20	0.01
HFC-227	99.89

EXAMPLE XXIV

Beclomethasone Dipropionate	0.1
Tween 20	0.01
HFC-227	99.89

EXAMPLE XXV

Mometasone Furoate	0.1
Tween 20	0.01
Oleic Acid	0.0005
HFC-227	99.8895

EXAMPLE XXVI

Beclomethasone Dipropionate	0.1
Tween 20	0.01
Oleic Acid	0.0005
HFC-227	99.8895

EXAMPLE XXVII

Mometasone Furoate	0.1
Miglyol 812	9
Oleic Acid	0.005
Tetronic 150 R1	0.01
HFC-227	90.885

EXAMPLE XXVIII

Beclomethasone Dipropionate	0.1
Miglyol 840	9
Oleic Acid	0.005
Pluronic L121	0.01
HFC-227	90.885

EXAMPLE XXIX

	A	B
Oleic Acid	0.001	0.01
Mometasone Furoate	0.1	0.1
Miglyol 812	1.0	10.0
HFC 227	98.8	89.8

EXAMPLE XXX

	A	B
Pluronic L121	0.1	0.1
Beclomethasone Dipropionate	0.1	0.1
Miglyol 812	1.0	10.0
HFC 227	98.8	89.8

EXAMPLE XXXI

	A	B
Beclomethasone Dipropionate	0.1	0.1
Miglyol 812	1.0	10.0
HFC 227	98.9	89.9

EXAMPLE XXXII

	A	B
Beclomethasone Dipropionate	0.1	0.1
PEG 400	1.0	10.0
HFC 227	98.9	89.9

EXAMPLE XXXIII

Beclomethasone Dipropionate	0.1
Ethanol	5
HFC 227	94.9

While the examples above have been directed at albuterol, albuterol sulfate, mometasone furoate, beclomethasone dipropionate and beclomethasone dipropionate clathrates, it is contemplated that other orally or nasally administered medicaments could be utilized. Similarly, it is contemplated that excipients and surfactants other than those exemplified may be utilized.

The descriptions of the foregoing embodiments of the invention have been presented for the purpose of illustration and description. They are not intended to be exhaustive or to limit the invention to the precise forms disclosed, and obviously many modifications and variations are possible in light of the above teaching. The embodiments were chosen and described in order to best explain the principles of the invention and its practical application to thereby enable others skilled in the art to best utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. It is intended that the scope of the invention be defined by the claims appended hereto.

Claims

1. An aerosol formulation comprising:
   A. an effective amount of a medicament;
   B. 1,1,1,2,3,3,3 heptafluoropropane;
   C. an excipient selected from a propylene glycol diester of a C_6-C_{12} fatty acid and a triglyceride ester of a C_6-C_{12} fatty acid; and
   D. optionally, one or more components selected from one or more of the following:
      surfactants;
      preservatives;
      buffers;
      antioxidants;
      sweeteners; and
      taste masking agents.

2. A formulation according to claim 1 wherein the medicament is selected from albuterol; mometasone furoate; beclomethasone dipropionate; isoproterenol; heparin; terbutaline; rimiterol; perbuterol; disodium cromoglycate; isoprenaline; adrenaline; pentamidine; ipratropium bromide; and salts and clathrates thereof.

3. A formulation according to claim 2 wherein the medicament is selected from albuterol; albuterol sulfate; beclomethasone dipropionate; bechlomethasone dipropionate clathrates; and mometasone furoate.

4. A formulation according to any preceding claim containing 0.01 to 1 percent by weight medicament.

5. A formulation according to claim 4 containing 0.03 to 0.7 percent by weight medicament.

6. A formulation according to claim 5 containing 0.05 to 0.5 percent by weight medicament.

7. A formulation according to any preceding claim wherein the medicament is a powder having a mean particle size of 1 to 5 microns.

8. A formulation according to any preceding claim wherein the excipient is a diester or triester of C_8-C_{12} fatty acid.

9. A formulation according to any preceding claim comprising 1 to 50 percent by weight excipient.

10. A formulation according to Claim 9 comprising 1 to 10 percent by weight excipient.

11. A formulation according to any preceding claim for medical use.

12. A formulation according to any preceding claim and comprising a medicament selected from albuterol, mometasone furoate, beclomethasone dipropionate, and salts and clathrates thereof, for the treatment of asthma in mammals.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 10 2113

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
D,Y	EP-A-0 384 371 (HOECHST AKTIENGESELLSCHAFT) * the whole document * * page 4 - page 5; examples 3,4 *	1-12	A61K9/72
Y	DEUTSCHE APOTHEKER ZEITUNG, vol.131, no.7, 14 February 1991, STUTTGART (DE) pages 263 - 269, XP173520 M. KELLER 'pharmazeutische aerosole' * page 265; table 1 * * page 265, column 1, paragraph 2 *	1-12	
Y	DE-A-32 46 081 (G. POHL-BOSKAMP GMBH & CO) * page 3, line 13 - line 29 * * page 5; example 1 *	1-12	
Y	EP-A-0 240 484 (BURGHART) * page 18 - page 19; example 2 *	1-12	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 March 1995	Benz, K

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C04)